Review Article

MIS-C is likely to be distinct from Kawasaki disease based on current studies: a narrative review

Chaozhong Tan, Fang Liu

Cardiovascular Center, Children's Hospital of Fudan University, Shanghai, China

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Correspondence to: Fang Liu, MD. Children's Hospital of Fudan University, 399 Wanyuan Road, Cardiovascular Center, Shanghai, China. Email: liufang@fudan.edu.cn.

Background and Objective: Children with SARS-CoV-2 infection were paid little attention to during the early stages of the outbreak because of low morbidity as well as mild clinical symptoms. Since late April 2020, reports regarding Kawasaki-like syndrome and hyperinflammatory response in children associated with COVID-19 have rapidly emerged. Till now, no certain relationship between multisystem inflammatory syndrome in Children (MIS-C) and Kawasaki Disease (KD) has been determined, which should be explored through continuous study.

Methods: In order to synthesize key findings for the objectives of this review, we searched English literature published up to November 16, 2020 using PubMed with the following keywords: Kawasaki disease 2020, Kawasaki-like disease, MIS-C, PIMS, PMIS and PIMS-TS.

Key Content and Findings: Based on current researches, KD is regarded as an immune disorder induced by multiple unidentified pathogens, while MIS-C is confirmed to be associated with the infection of COVID-19. In addition, KD is popular in East Asian children under 3 years old, while MIS-C is reported more in older adolescents from Europe and North America. On the basis of multiple cohort studies, gastrointestinal symptoms, mechanical ventilation and inotropic support are more common in MIS-C. Instead, coronary arterial damage is more pronounced in KD. Moreover, the treatment regimen for MIS-C is more aggressive than KD because the cytokine storm is more violent and lasting.

Conclusions: MIS-C is likely to be a distinct immunopathogenic illness associated with SARS-CoV-2 based on current studies, which could be used as a reference to help us better understand KD. In addition, MIS-C is an emerging syndrome for pediatricians, so the lack of relevant knowledge may result in under-diagnosis. Some individuals may fulfill full or partial criteria for KD but all should be reported if they meet the case definition for MIS-C.

Keywords: Multisystem inflammatory syndrome in children (MIS-C); Kawasaki disease (KD); coronavirus disease 2019 (COVID-19)

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Introduction

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China. To date, COVID-19 has affected patients across all age groups, with a wide range of illness severity from asymptomatic carriers to severe multi-organ dysfunction and even death. It seemed that children comprised only a small proportion of overall confirmed COVID-19, which was reported as 1% in China (1),

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	From November 9, 2020 to November 16, 2020
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	Kawasaki disease 2020, Kawasaki-like disease, MIS-C, PIMS, PMIS and PIMS-TS
Timeframe	Literature published up to November 16, 2020
Inclusion and exclusion criteria (study type, language restrictions etc.)	Study type: Review, Systematic Review, Clinical Trial and Randomized Controlled Trial Language restrictions: English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All the authors conducted the selection after discussion.
Any additional considerations, if applicable	None

1.2% in Italy (2), and 1.7% in the U.S. (3). Moreover, the initial reports showed that children experienced less severe disease than adults. Seventy-three percent of pediatric patients presented symptoms of fever, cough or shortness of breath, compared with 93% of adults aged 18–64 years during the same period (3). Over 90% of pediatric patients were diagnosed as asymptomatic, mild or moderate disease (4-6). In comparison, in an adult cohort of symptomatic patients with COVID-19, 14% had severe disease and 5% became critically ill with multi-organ failure (7).

However, the first known case of concurrent COVID-19 and Kawasaki disease (KD) was reported in Stanford, U.S. (8). Shortly after, it was successively reported in Europe that children with active or recent infection could also present with a severe inflammatory syndrome whose features overlapped that of KD (9-13). On April 26, the National Health Service in the United Kingdom (NHS UK) issued an alert to highlight a rise in such cases (14). Subsequently, the Royal College of Paediatrics and Child Health (RCPCH), US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) announced the case definition respectively (15-17). Among them, the case definition proposed by WHO is widely used. Children and adolescents 0–19 years of age with fever ≥3 days is the preliminary case definition. The case definition includes two of the following clinical findings: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated d-Dimers); acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain). MIS-C patients also appear elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. Besides, there should be no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. It's worth noting that the RT-PCR, serology, or antigen test could be negative. The syndrome has been referred to by many names, including multisystem inflammatory syndrome in Children (MIS-C), Pediatric Inflammatory Multisystem Syndrome (PIMS) and PIMS temporally associated with SARS-CoV-2 infection (PIMS-TS). For consistency, we will use MIS-C in this review. We present the following article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-20-113/rc).

Objective

The similarities between MIS-C and KD have led to the hypothesis that MIS-C was a form of KD. With more literature reported, we found that there were many differences between the two. Our main objective was to review relevant literature on the differences between MIS-C and KD.

Methods

We conducted a literature search using online database PubMed (*Table 1*), specifically for papers related to the severe inflammatory syndrome which is similar to Kawasaki

disease during COVID-19 epidemic. The key search terms included Kawasaki disease 2020, Kawasaki-like disease, MIS-C, PIMS, PMIS and PIMS-TS.

Discussion

Epidemiology

Current evidence supported a more explicit causal link between MIS-C and SARS-CoV-2, as compared to KD and its possible pathogen. In several cohort studies, SARS-CoV-2 PCR and IgG serology were positive for 22–50% and 75–94% (2,12,18). Besides, the number of MIS-C cases was proportional to the percentage testing positive for SARS-CoV-2 in the local population, with a 4-week time window. It was consistent with the fact that a median interval of 25 days was reported between the onset of COVID-19 symptoms and hospitalization for MIS-C (19). Also, the geographical distribution of MIS-C cases was comparable to the one of all-ages COVID-19 hospitalizations, according to nationwide surveillance of France (20). By contrast, despite extensive effort to identify the triggers for the inflammatory cascade in KD, the unifying etiological agent remains elusive (21).

The incidence of MIS-C and KD varied markedly among different ethnic groups. It was observed that African ancestry made up more than half of MIS-C patients in most cohorts (10,11,13). In the U.S., black or Hispanic made up the majority of MIS-C cases, whose percentage was similar to that of children diagnosed with COVID-19. But the morbidity in black or Hispanic was higher than their proportion of the U.S. population overall (19), which may be explained by the social determinants of health (22). KD presents different racial characteristics of incidence, which is prevalent in East Asia descent, especially in Japanese (23). However, there was only one case report confirming MIS-C in South Korea (24) and no such case was reported in China and Japan, which suggests that the genetic susceptibility of MIS-C and KD may be different.

Clinical findings

In the beginning, these cases were simply regarded as KD accompanied by SARS-CoV-2 infection. Since MIS-C patients partially met the diagnostic criteria of typical KD [only about 15% MIS-C patients appear extremity changes and cervical lymphadenopathy (25)], the prevalence of incomplete KD ascended from 15–36.2% to 45.9% in a recent review (26). With further understanding of MIS-C, clinicians gradually realized that although clinical manifestations of MIS-C and KD may be overlapping, they appeared to be two distinct clinical entities.

Firstly, MIS-C was more prevalent in older children. The median age of MIS-C cases was 7–11 years (9,18-20) and the upper age limit was 18–21 years in case definitions formulated by RCPCH, CDC and WHO (15-17). Whereas, the median age of KD was 3 years in Italy (9); 1.8 years in Shanghai (27) and more than 80% of KD patients were younger than 5 years old. According to a recent epidemiological investigation in Japan, the incidence of KD was highest in children between 9 and 11 months of age, after which the incidence gradually decreased with advancing age (28). Besides, vomiting, diarrhea and abdominal pain were more common in MIS-C. More than 80% of MIS-C patients appeared gastrointestinal symptoms (11-13,29), which was relatively rare in KD. Moreover, as high as 48–83% of MIS-C patients developed signs of systemic hypoperfusion or shock (18-20). In comparison, severe complications, which is called Kawasaki diseases shock syndrome (KDSS) and macrophage activating syndrome (MAS), only account for 6% (30) and 1.11% in KD overall (31). Accordingly, higher levels of NT-proBNP and troponin were detected in MIS, which are indicative of myocardial dysfunction and injury respectively (19,32). With regard to coronary artery lesions (CAL), the prevalence of CAL was 24.6% in untreated KD patients (33); 6.5–9.1% when received timely treatment (27,28). Whereas, the incidence of CAL varied from 8% to 24% in MIS-C cohorts (11,13,19) based on the limited number of cases. DCBLD2, a biomarker of vascular remodeling, was detected more elevated in KD than MIS-C. Higher plasma levels of endoglin were also measured in KD (34). These findings supported that arterial damage was more pronounced in KD. Large sample studies or meta-analyses are needed.

The laboratory findings were also different in MIS-C and KD patients. Almost all KD patients exist obvious neutrophilia in the acute stage, while in MIS-C patients neutrophil count could increase (13,18,32) or decrease (25). Besides, it has been found that MIS-C presents with raised fibrinogen, raised D-dimer and low platelets in the acute phase, which normalized by convalescence, suggesting a procoagulant state in the acute phase. Although acute inflammation is common in Kawasaki disease, the procoagulant state seen in MIS-C patients is not a common feature of Kawasaki disease (25). Furthermore, in

multiple MIS-C cohort studies, the average blood sodium concentration was 130 mmol/L, and the average plasma albumin concentration was 21 g/L (11-13), which suggested more generalized and more severe vasculitis in MIS-C.

Pathogenesis

Although the mechanism of MIS-C is still under investigation, pieces of evidence (elevated cytokine levels, acute systemic inflammatory effects and secondary organ dysfunction), as well as beneficial effects of immunosuppressant agents in affected patients, predict that cytokine storm is likely a key pathophysiologic process of MIS-C (35). There is immune dysregulation in KD as well, but the hyperinflammatory immune state is different in terms of T cell differentiation and cytokine storm formation (34). Another hypothesized mechanism of MIS-C involves autoimmunity due to molecular mimicry between SARS-CoV-2 and a self-antigen. There is a similar theory attempting to illuminate the pathophysiology of KD that antiendothelial autoantibodies (AECAs) could be produced during an acute immune response to a viral infection, probably at mucosal surfaces and focused around IgA-producing plasma cells (36,37). Besides, the result of VirScan (38), a high throughput method for testing IgG to different viruses, showed that MIS-C patients were lack of antibodies to common coronavirus while KD showed evidence of IgG against various viruses (34). It refuted the hypothesis that prior immunity to other viruses could modulate their responses to SARS-CoV-2 infection and give rise to hyperinflammation in MIS-C (39). However, the relevance between antibodies and viruses remains to be determined.

Treatment

The current first-line therapy for KD is the combination of high dose intravenous immunoglobulin (IVIG) and aspirin. 82.2–91.6% of KD patients are sensitive to IVIG and recover quickly (27,28). However, in a MIC-C cohort, mechanical ventilation and inotropic support were needed in 80% of patients and extracorporeal membrane oxygenation (ECMO) support was needed in 28% of patients. Besides, the cytokine storm of MIS-C is so fierce that traditional treatment cannot stop inflammation in time. Thus, it is recommended to adopt a more aggressive treatment regimen in MIS-C. In addition to IVIG, glucocorticoids were usually added for immunomodulatory therapy at the early stage. For those who failed initial treatments or showed symptoms of severe illness, biologic drugs, such as IL-1 inhibitors (Anakinra), IL-6 inhibitors (Tocilizumab) or TNF-α inhibitors (Infliximab), could be considered depending on the condition of the individual. As MIS-C patients tend to appear significant cardiac involvement, appropriate laboratory examination (BNP and troponin) and imaging examination (echocardiogram) with cardiology input are essential for children suspected to have MIS-C, which are beneficial to estimate therapeutic effect and prognosis. For children with coagulation disorders such as elevated D-dimer, especially with coronary artery lesions, unfractionated heparin (5–10 IU/kg.h) or low-molecular-weight heparin (LMWH) can be added, combined with low-dose aspirin or other anti-platelet regimes. Concerning antiviral treatment, the risks of potentially serious adverse events must be taken into account and decisions should be based on considerations of risks versus benefits for individual patients (40). Among the options available, Remdesivir could be the first-choice drug for COVID-19 in children (41). As the evidence base for MIS-C is evolving rapidly, there is no recognized guideline and the treatment regimen should be adjusted according to the individual clinical circumstances of patients and the resources available to clinicians.

Limitations

Restricted by the assessment of the limited number of cohorts, our conclusions are not comprehensive enough. More cohort studies are required. Besides, most current study only focused on the clinical findings.

Future research

Cell functionality and mechanisms of immune abnormalities remain uncertain, which should be considered in future studies.

Conclusions

Taken together, MIS-C is likely to be a distinct immunopathogenic illness associated with SARS-CoV-2 based on current studies, which could be used as a reference to help us better understand KD. In addition, MIS-C is an emerging syndrome for pediatricians so the lack of relevant knowledge may result in under-diagnosis. Some individuals may fulfill full or partial criteria for KD but all should be

reported if they meet the case definition for MIS-C.

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Footnote

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